

AMENDMENT

In the Claims

The following Listing of Claims, in which deleted text appears as ~~struck through~~ and inserted text appears underlined, will replace all prior listings, and versions, of claims in the application.

Listing of Claims

Claim 1 (cancelled)

Claim 2 (currently amended): The method of claim 68, wherein ~~the animal~~ said subject is a human.

Claim 3 (currently amended): The method of claim 2, wherein ~~the short-term formulation of interferon is~~ said one or more interferons formulated for short-term delivery are selected from the group consisting of natural ~~or~~ and recombinant alpha, beta, consensus, gamma, leukocyte, omega, ~~or~~ and tau interferon ~~or~~ and versions thereof to which polyethylene glycol or a polyethylene glycol-fatty acid moiety has been is attached by covalent or non-covalent bonding, or mixtures thereof.

Claim 4 (currently amended): The method of claim 3, wherein ~~the~~ said interferon-responsive ~~disease disorder~~ is selected from the group consisting of viral hepatitis C, viral hepatitis B, condyloma accuminata, hairy cell leukemia, malignant melanoma, follicular lymphoma, ~~AID's~~ AIDS-related Kaposi's sarcoma, multiple sclerosis, chronic granulomatous disease, pulmonary fibrosis, and tuberculosis.

Claim 5 (currently amended): The method of claim 3, wherein ~~the~~ said interferon-responsive ~~disease disorder~~ is selected from the group consisting of viral hepatitis C, viral hepatitis B, condyloma accuminata, hairy cell leukemia, malignant melanoma, follicular lymphoma, ~~AID's~~ and AIDS-related Kaposi's sarcoma; ~~and at least one interferon is~~ said one or more interferons formulated for short-term delivery are selected from the group consisting of natural ~~or~~ and recombinant alpha, consensus, leukocyte, omega ~~or~~ and tau interferon ~~or~~ and versions thereof to which polyethylene glycol or a polyethylene glycol-fatty acid moiety ~~has been~~ is attached by covalent or non-covalent bonding, or mixtures thereof.

Claim 6 (currently amended): The method of claim 3, wherein ~~the~~ said interferon-responsive ~~disease disorder~~ is selected from the group consisting of chronic granulomatous disease, pulmonary

fibrosis, and tuberculosis; and ~~at least one interferon is~~ said one or more interferons formulated for short-term delivery are selected from the group consisting of natural ~~or~~ and recombinant gamma interferon ~~or~~ and a version thereof to which polyethylene glycol or a polyethylene glycol-fatty acid moiety has been is attached by covalent or non-covalent bonding.

Claim 7 (currently amended): The method of claim 3, wherein ~~the~~ said interferon-responsive disorder disease is multiple sclerosis; and ~~at least one interferon is~~ said one or more interferons formulated for short-term delivery are selected from the group consisting of natural or recombinant alpha, beta, consensus, leukocyte, omega ~~or~~ and tau interferon ~~or~~ and versions thereof to which polyethylene glycol or a polyethylene glycol-fatty acid moiety has been is attached by covalent or non-covalent bonding, or mixtures thereof.

Claim 8 (currently amended): The method of claim 3, wherein ~~the same interferon~~ said one or more interferons formulated for ~~is administered in the short-term delivery are the same or different as said one or more interferons formulation as is administered in the subsequent~~ formulated for long-term delivery formulation of interferon.

Claim 9 (currently amended): The method of claim 2, wherein ~~a first interferon~~ said one or more interferons is administered as a ~~formulated for short-term formulation delivery and a different interferon said one or more interferons is subsequently administered in the~~ formulated for long-term formulation delivery are independently selected from the group consisting of natural or recombinant alpha, beta, consensus, leukocyte, omega ~~or~~ and tau interferon ~~or~~ and versions thereof to which polyethylene glycol or a polyethylene glycol-fatty acid moiety is attached.

Claim 10 (currently amended): The method of claim 2, wherein the short-term formulation and the long-term formulation are the same ~~formulation~~.

Claim 11 (currently amended): The method of claim 2, wherein the short-term formulation and the long-term formulation are ~~two~~ different ~~formulations~~.

Claim 12 (currently amended): The method of claim 2, wherein ~~more than one interferon is administered for~~ said one or more interferons formulated for short-term use, delivery is a plurality of

~~interferons and each short-term formulation is interferon being in the same formulation or in different short term formulations.~~

Claim 13 (currently amended): The method of claim 2, wherein ~~more than one interferon is administered for~~ said one or more interferons formulated for long-term use, delivery is a plurality of interferons and each long-term formulation is ~~interferon being in the same formulation or with in different long term formulations.~~

Claim 14 (currently amended): The method of claim 2, ~~wherein~~ in which there is an overlap of in ~~the~~ administration of the short-term formulation and the long-term formulation.

Claim 15 (currently amended): The method of claim 2, wherein the rates of short-term and long term delivery are ~~controlled release dosage per time unit selected for the long term formulation is about substantially equivalent to the dosage release over the time unit for the short term formulation.~~

Claim 16 (currently amended): The method of claim 2, wherein the rates of short-term delivery and long term delivery are not substantially equivalent ~~controlled release dosage per time unit selected for the long term formulation is different than that administered with the short term formulation.~~

Claim 17 (currently amended): The method of claim 2, wherein the short-term formulation is delivered by ~~an~~ injection, ~~an~~ infusion, implant an implantable system, a transdermal delivery system transdermally, an oral formulation orally, non-oral parenteral formulation parenterally, or by an inhalational device.

Claim 18 (cancelled)

Claim 19 (currently amended): The method of claim 13, wherein ~~at least one of the long term formulations of interferon is~~ said one or more interferons formulated for long-term delivery are selected from the group consisting of natural ~~or and~~ recombinant alpha, beta, consensus, gamma, leukocyte, omega, ~~or and~~ tau interferon, ~~or and~~ versions thereof to which polyethylene glycol or a polyethylene glycol-fatty acid moiety ~~has been~~ is attached by ~~covalent or non-covalent bonding, or mixtures thereof.~~

Claim 20 (currently amended): The method of claim 19, wherein ~~the interferon is~~ said one or more interferons formulated for long-term delivery are selected from the group consisting of natural ~~or~~

and recombinant omega interferon ~~or~~ and versions thereof to which polyethylene glycol or a polyethylene glycol-fatty acid moiety ~~has been~~ is covalently or non-covalently attached ~~by covalent or non-covalent bonding, or mixtures thereof.~~

Claim 21 (cancelled)

Claim 22 (currently amended): The method of claim 74, wherein ~~the animal~~ said individual subject is a human.

Claim 23 (cancelled)

Claim 24 (currently amended): The method of claim 22, wherein ~~the~~ said interferon-responsive disease disorder is selected from the group consisting of viral hepatitis C, viral hepatitis B, viral hepatitis D, condyloma accuminata, hairy cell leukemia, malignant melanoma, multiple myeloma, follicular lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, chronic myelogenous leukemia, basal cell carcinoma, mycosis fungoides, carcinoid syndrome, superficial bladder cancer, renal cell cancer, colorectal cancer, laryngeal papillomatosis, actinic keratosis, Kaposi's sarcoma, multiple sclerosis, chronic granulomatous disease, pulmonary fibrosis, and tuberculosis.

Claim 25 (currently amended): The method of claim 22, wherein ~~the~~ said interferon-responsive disease disorder is selected from the group consisting of viral hepatitis C, viral hepatitis B, viral hepatitis D, condyloma accuminata, hairy cell leukemia, malignant melanoma, multiple myeloma, follicular lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, chronic myelogenous leukemia, basal cell carcinoma, mycosis fungoides, carcinoid syndrome, superficial bladder cancer, renal cell cancer, colorectal cancer, laryngeal papillomatosis, actinic keratosis, Kaposi's sarcoma[,]; and said at least one interferon is selected from the group consisting of natural ~~or~~ and recombinant alpha, consensus, leukocyte, omega ~~or~~ and tau interferon ~~or~~ and versions thereof to which polyethylene glycol or ~~glycol or~~ a polyethylene glycol-fatty acid moiety ~~has been~~ is covalently or non-covalently attached ~~by covalent or non-covalent bonding.~~

Claim 26 (currently amended): The method of claim 22, wherein ~~the~~ said interferon-responsive disease disorder is selected from the group consisting of chronic granulomatous disease, pulmonary fibrosis, and tuberculosis; and said at least one interferon is selected from the group consisting of natural

~~or and~~ recombinant gamma interferon ~~or and~~ a version thereof to which polyethylene glycol ~~or glycol~~ or a polyethylene glycol-fatty acid moiety ~~has been~~ is covalently or non-covalently attached by covalent or non-covalent bonding.

Claim 27 (currently amended): The method of claim 22, wherein ~~the disease~~ said interferon-responsive disorder is selected from the group consisting of multiple sclerosis; and said at least one interferon is selected from the group consisting of natural or and recombinant alpha, beta, consensus, leukocyte, omega or and tau interferon or and versions thereof to which polyethylene glycol or a polyethylene glycol-fatty acid moiety ~~has been~~ is covalently or non-covalently attached by covalent or non-covalent bonding, or mixtures thereof.

Claim 28 (cancelled)

Claim 29 (currently amended): The method of claim 22, wherein ~~a first~~ said at least one interferon is administered as a formulated for short-term delivery formulation and ~~a different~~ said at least one interferon is administered as the formulated for long-term formulation delivery are independently selected from the group consisting of natural and recombinant alpha, beta, consensus, leukocyte, omega and tau interferon and versions thereof to which polyethylene glycol or a polyethylene glycol-fatty acid moiety is covalently or non-covalently attached, and mixtures thereof.

Claim 30 (currently amended): The method of claim 22, wherein the short-term formulation and the long-term formulation are the same ~~formulation~~.

Claim 31 (currently amended): The method of claim 22, wherein the short-term formulation ~~differs from~~ and the long-term formulation are different.

Claim 32 (currently amended): The method of claim 22, wherein ~~more than one interferon~~ said at least one interferon formulated is administered for short-term delivery use, is a plurality of interferons and each short-term interferon being in the same formulation is the same or in different short term formulations.

Claim 33 (currently amended): The method of claim 22, wherein ~~more than one interferon is administered for~~ said at least one interferon formulated for long-term delivery is a plurality of interferons

~~and use, each interferon being in the same long-term formulation is the same or in different long-term delivery systems.~~

Claim 34 (cancelled)

Claim 35 (currently amended): The method of claim 22, wherein the rates of short-term and long-term delivery are controlled release dosage per time unit selected for the long-term formulation is about substantially equivalent to the dosage release over the time unit for the short-term formulation.

Claim 36 (currently amended): The method of claim 22, wherein the rates of short-term delivery and long term delivery are not substantially equivalent controlled release dosage per time unit selected for the long-term formulation is different that that administered with the short-term formulation.

Claim 37 (currently amended): The method of claim 23, wherein the short-term formulation is selected from delivered by an injection, an infusion, implant an implantable system, transdermally a transdermal delivery system, an oral formulation orally, parenterally non-oral parenteral administration, or by inhalation an inhalational device.

Claim 38 (currently amended): The method of claim 37, wherein the said at least one interferon formulated for short-term formulation of interferon delivery is selected from the group consisting or natural ~~or~~ and recombinant alpha, beta, consensus, gamma, leukocyte, omega, ~~or~~ and tau interferon, ~~or~~ and versions thereof to which polyethylene glycol or a polyethylene glycol-fatty acid moiety ~~has been~~ is attached ~~by covalent or non-covalent bonding, or~~ and mixtures thereof.

Claim 39 (cancelled)

Claim 40 (currently amended): The method of claim 33 wherein said at least one interferon formulated for of the long-term formulations of interferon delivery is selected from the group consisting of natural ~~or~~ and recombinant alpha, beta, consensus, gamma, leukocyte, omega, ~~or~~ and tau interferon, ~~or~~ and versions thereof to which polyethylene glycol or a polyethylene glycol-fatty acid moiety ~~has been~~ is attached ~~by covalent or non-covalent bonding, or~~ and mixtures thereof.

Claim 41 (currently amended): A method of ~~manufacturing making~~ a long-term drug delivery device for delivering a drug over time, which method comprises, comprising:

a) determining a therapeutic and tolerable pharmacokinetic profile for a drug therapy in a subject by administering one or more drugs formulated for short-term delivery to said subject and monitoring said subject for therapeutic and adverse effects; ~~preparing a standard rate long-term delivery device designed for delivery of a drug at a relatively constant rate over time, the rate being determined to be a unit rate designed for a patient to receive a standard dosage rate to at a disease state in the patient treatable over time by the drug, and~~

b) preparing a ~~an internally presentable, not externally programmable pump containing said one or more drugs formulated for reduced rate long-term delivery in which said drugs are released from said pump device designed for delivery of the same drug at a relatively constant first dosage rate; and over time, which rate is a fraction of the standard dosage rate;~~

c) preparing a second internally presentable, not externally programmable pump for long-term delivery in which said one or more drugs are released at a fraction of said first dosage rate,

wherein each pump, alone or in combination, substantially achieves said pharmacokinetic profile during said long-term delivery wherein each device releases the drug from an implantable pump that is not externally programmed and is suitable for internal presentation to a patient in need thereof alone or in combination with an identical device or the other device, depending on the dosage rate or fractional dosage rate determined to be appropriate for the patient.

Claim 42 (currently amended): The method of claim 41, wherein the ~~rate of delivery of the drug from the reduced rate device~~ fractional dosage rate is about fifty percent of the rate of delivery from the standard ~~said first dosage rate device.~~

Claim 43 (currently amended): The method of claim 41, ~~which method further comprises~~ further comprising:

d) preparing dosing instructions for adjusting the rate of administration of ~~the drug~~ said one or more drugs formulated for long-term delivery by employing one or a combination of the first or fractional dosage rate pumps devices to achieve the desired release rate of the drug for a patient depending on the patient's needs over time.

Claim 44 (currently amended): The method of claim 41, wherein ~~the drug is an interferon~~ said one or more drugs is one or more interferons.

Claim 45 (currently amended): The method of claim 44, wherein ~~the interferon is~~ said one or more interferons are selected from the group consisting of natural ~~or~~ and recombinant alpha, beta, consensus interferon, gamma, leukocyte, omega, ~~or~~ and tau interferon, ~~or~~ and versions thereof to which polyethylene glycol or a polyethylene glycol-fatty acid moiety ~~has been~~ is attached ~~by covalent or non-covalent bonding, or mixtures thereof.~~

Claim 46 (currently amended): The method of claim 41, in which said one or more drugs are suitable for treating ~~wherein the disease state is~~ an interferon-responsive disorder ~~disease~~.

Claim 47 (currently amended): The method of claim 46, wherein ~~the~~ said interferon-responsive disorder ~~disease~~ is selected from the group consisting of viral hepatitis C, viral hepatitis B, viral hepatitis D, condyloma accuminata, hairy cell leukemia, malignant melanoma, multiple myeloma, follicular lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, chronic myelogenous leukemia, basal cell carcinoma, mycosis fungoides, carcinoid syndrome, superficial bladder cancer, renal cell cancer, colorectal cancer, laryngeal papillomatosis, actinic keratosis, Kaposi's sarcoma, multiple sclerosis, chronic granulomatous disease, pulmonary fibrosis, and tuberculosis.

Claim 48 (cancelled)

Claim 49 (currently amended): The method of claim 45 ~~46~~ wherein ~~the disease~~ said interferon-responsive disorder is hepatitis C; and ~~the interferon~~ said one or more drugs is omega interferon.

Claim 50 (currently amended): The method of claim 45 ~~46~~ wherein ~~the disease~~ said interferon-responsive disorder is hepatitis C and ~~the interferon~~ and said one or more drugs is an alpha interferon.

Claim 51 (currently amended): The method of claim 45 ~~46~~ wherein ~~the disease~~ said interferon-responsive disorder is hepatitis C and ~~the interferon~~ and said one or more drugs is a consensus interferon.

Claim 52 (currently amended): The method of claim 45 ~~46~~ wherein ~~the disease~~ said interferon-responsive disorder is hepatitis C and ~~the interferon~~ and said one or more drugs is a natural or recombinant interferon.

Claim 53 (currently amended): The method of claim 46, wherein ~~the~~ said interferon-responsive disease ~~disorder~~ is selected from the group consisting of chronic granulomatous disease, pulmonary

fibrosis, and tuberculosis; and said one or more drugs is one or more interferons selected from the group consisting of the interferon is natural or and recombinant gamma interferon or and a version thereof to which polyethylene glycol or a polyethylene glycol-fatty acid moiety has been is attached by covalent or non-covalent bonding and mixtures thereof.

Claim 54 (currently amended): The method of claim 44, wherein ~~the disease~~ said interferon-responsive disorder is selected from the group consisting of multiple sclerosis; and the interferon is said one or more drugs is one or more interferons selected from the group consisting of natural or and recombinant alpha, beta, consensus, leukocyte, omega or and tau interferon or and versions thereof to which polyethylene glycol or a polyethylene glycol-fatty acid moiety has been is attached by covalent or non-covalent bonding, or mixtures thereof.

Claims 55-67 (cancelled)

Claim 68 (currently amended): A method ~~for the treatment of~~ treating an interferon-responsive disorder in a ~~warm-blooded animal, which method comprises~~ subject, comprising:

administering a) determining a well-tolerated, therapeutic pharmacokinetic profile for interferon therapy in a subject by administration of one or more interferons formulated for short-term delivery to the animal said subject and monitoring said subject for therapeutic and adverse effects at least one interferon formulated for short term use; and

adjusting the dosage with the short term formulation to increase therapeutic response;

subsequently selecting a dosage to be administered as a b) administering to said subject using at least one internally presented, not externally programmable pump one or more interferons formulated for long-term delivery in which said interferons are released from said pump at a formulation having a controlled rate of release over time; and that substantially achieves said pharmacokinetic profile during said long-term delivery

thereafter administering the long term formulation to release the interferon at a controlled rate over time;

wherein the long term formulation of interferon is released from an internally presented implantable pump that is not externally programmed, and further wherein the short term formulation of interferon is not released from the internally presented implantable pump from which the long term formulation is released.

Claim 69 (currently amended): The method of claim 68, further comprising:

c) the step of optionally adjusting the level amount of said one or more interferons interferon released administered to said subject with an additional long-term formulation of one or more interferons to further maximize therapeutic response.

Claim 70 (currently amended): The method of claim 68, wherein ~~the pump releases an interferon at a~~ said rate is a substantially fixed rate.

Claim 71 (currently amended): The method of claim 68, wherein ~~the interferon is released from a plurality of internally presented implantable~~ said at least one pump is a plurality of said pumps that are not externally programmed.

Claim 72 (currently amended): The method of claim 71, wherein each pump releases ~~an interferon~~ said one or more interferons at a substantially fixed rate.

Claim 73 (currently amended): The method of claim 68, wherein ~~the implantable~~ said pump is an osmotic pump.

Claim 74 (currently amended): A method ~~for~~ of individualizing doses of interferon in the treatment of an ~~interferon-responsive disorders in a warm blooded animal, which method comprises disorder, comprising:~~

a) defining a unit dosage of at least one interferon by administering said at least one interferon[,] formulated for short-term use, in delivery to a plurality of the animals subjects to determine the most common optimal dosage; and

b) administering to a subject using one or more internally presented, not externally programmable pumps at least one unit dosage of at least one interferon formulated for long-term delivery and optionally with one or more fractional dosages formulated for long-term delivery

wherein the at least one unit dosage optionally in combination with one or more fractional dosages released from said one or more pumps substantially achieves the unit dosage defined in step a) during said long-term delivery

adjusting the dosage with the short term formulation to increase therapeutic response;
determining the most commonly identified optimal dosage over time in a sufficiently large population of the animals to define such dosage as a unit dose;

~~subsequently, defining a long term formulation for delivering such dosage over time as more unit dose or a fraction thereof, such that, in aggregate, the optimal dosage identified during dosing with the short term formulation can be approximated with the unit dose or fractional unit dose combination using the long term formulation to deliver the interferon in a controlled dose over time;~~

~~selecting a dosage to be administered to an individual animal with a long term delivery; and thereafter administering the long term dosage with a long term delivery system, wherein said long term delivery system releases interferon from an internally presented implantable pump that is not externally programmable, and further wherein the short term formulation of interferon is not released from the internally presented implantable pump from which the long term formulation is released.~~

Claim 75 (currently amended): The method of claim 74, further comprising:

~~c) the step of adjusting the one or more unit or fractional dosages dosage administered to said individual subject over time with the long term formulation to further maximize therapeutic response.~~

Claim 76 (currently amended): The method of claim 74, wherein ~~the long term delivery system releases~~ said one or more pumps release interferon at a substantially fixed rate.

Claim 77 (currently amended): The method of claim 41, wherein ~~the long term delivery device is designed to deliver interferon at a~~ said one or more pumps have fixed delivery rate rates.

Claim 78 (currently amended): The method of claim 3, wherein ~~the said one or more interferons formulated for long-term formulation of interferon is~~ delivery are selected from the group consisting of natural or and recombinant omega interferon or and versions thereof to which polyethylene glycol or a polyethylene glycol-fatty acid moiety has been is attached by covalent or non-covalent bonding, or mixtures thereof.

Claim 79 (currently amended): The method of claim 2, ~~wherein in which~~ there is no overlap of in administration of the short-term formulation and the long-term formulation.

Claim 80 (currently amended): The method of claim 68, wherein ~~the said long-term formulation is released over a period of~~ delivery is for at least ~~approximately~~ about one month.

Claim 81 (currently amended): The method of claim 68, wherein ~~the said long-term formulation is released over a period of~~ delivery is for at least ~~approximately~~ about a quarter year.

Claim 82 (currently amended): The method of claim 22, wherein ~~the long-term formulation of interferon is said at least one interferon formulated for long-term delivery is selected from the group consisting of~~ natural ~~or~~ and recombinant omega interferon ~~or~~ and versions thereof to which polyethylene glycol or a polyethylene glycol-fatty acid moiety ~~has been~~ is attached ~~by covalent or non-covalent bonding, or mixtures thereof.~~

Claim 83 (currently amended): The method of claim 45, wherein ~~the interferon is said one or more interferons are selected from the group consisting of~~ natural ~~or~~ and recombinant omega interferon ~~or~~ and versions thereof to which polyethylene glycol or a polyethylene glycol-fatty acid moiety ~~has been~~ is attached ~~by covalent or non-covalent bonding, or mixtures thereof.~~

Claim 84 (new): The method of claim 68, wherein said one or more interferons formulated for short-term delivery are not released from the internally presented implantable pump from which said one or more interferons formulated for long-term delivery are released.

Claim 85 (new): The method of claim 71, wherein said at least one interferon formulated for short-term delivery are not released from the internally presented implantable pump from which said one interferon formulated for long-term delivery are released.

Claim 86 (new): A method of treating HCV, comprising: administering to a patient an amount of omega interferon effective to provide therapeutic benefit for at least 3 months, wherein the omega interferon is formulated in an implantable device that is not externally programmable that delivers the omega interferon at a constant rate for said at least 3 months.

Claim 87 (new): A method of treating HCV, comprising:

a) determining for a patient an amount of omega interferon that has a well-tolerated, therapeutic index for said patient; and

b) administering to said patient using one or more internally presented, not externally programmable pumps an amount of omega interferon effective to achieve said therapeutic index for a period of 3-12 months.

Claim 88 (new): A method of treating HCV, comprising:

- a) determining for a patient an amount of omega interferon that has a well-tolerated, pharmacokinetic profile for said patient; and
- b) administering to said patient using one or more internally presented, not externally programmable pumps an amount of omega interferon effective to achieve said pharmacokinetic profile for a period of 3-12 months.